NTP
National Toxicology Program

National Toxicology Program
Center for Phototoxicology (NCP)

Located at the

U.S. Food & Drug Administration's

National Center for Toxicological Research,

Jefferson Laboratories,

Jefferson, Arkansas

OUTLINE

- Stimulus for NCP
- Challenge, Purpose, Product
- Oversight
- Facilities and Operation
- Support
- Studies in NCP
- Future Directions

INTERAGENCY AGREEMENT – NTP AND FDA

"… to conduct mechanistic-based toxicity and carcinogenicity studies on FDA high priority chemicals nominated to the National Toxicology Program (NTP)..."

STIMULUS FOR NCP

Nomination of alpha hydroxy acids (~1998) to the NTP by FDA exposed deficiency regarding conduct of toxicology studies in presence of light.

Since humans are exposed simultaneously to terrestrial sunlight and chemicals (*e.g.* natural and anthropomorphic environmental chemicals, cosmetics, drugs) this deficiency needed to be addressed.

DEFINITIONS

Phototoxicity –
toxicity of a chemical when irradiated with electromagnetic radiation.

Photocarcinogenicity –
carcinogenicity of a chemical when irradiated with non-carcinogenic doses of electromagnetic radiation.

Photococarcinogenicity –
the effect of a chemical on carcinogenic doses of electromagnetic radiation.

NCP: CHALLENGE, PURPOSE, PRODUCTS

Challenge –
develop a multi-study, multi-user facility for testing the phototoxicity, photocarcinogenesis, and photococarcinogenesis of chemicals.

Purpose –
conduct toxicology studies on the interaction of light with chemicals.

Product –
(1) toxicological data for public health decisions, chemicals ± light; (2) NTP Technical Reports; (3) peer-reviewed scientific publications.

OVERSIGHT

NTP/FDA Toxicology Study Selection and Review Committee (TSSRC):
Biannual review of all NTP/FDA IAG studies, including NCP operation.

Peer-Review Working Group:
Photobiology and photophysics peer-review, regarding operation and direction of NCP (Aug. 2000; Sept. 2005)

FACILITIES AND OPERATION

Located at NCTR;

Occupies ~5000 ft^2

- 6 animal rooms, each max. of ~1000 mice,
- 1 multi-study exposure room,
- 1 control room

Paul C. Howard, PhD, Director

Mary D. Boudreau, PhD, Manager

Frederick A. Beland, PhD, Division Director

LIGHT PRODUCING DEVICES FOR IRRADIATION OF ANIMALS

Sunlight simulation:

6,500 Watt xenon arc solar simulators
(2 horizontal, 1 vertical)

Ultraviolet B light:

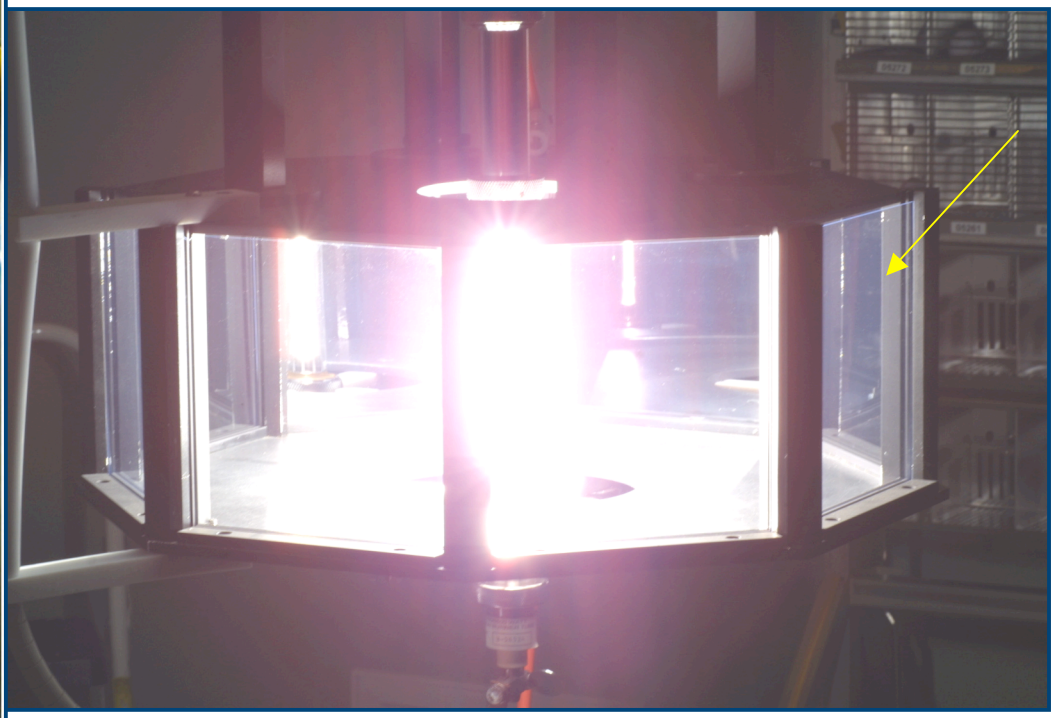
UVB fluorescent lamp exposure units
(1 horizontal, 1 vertical, 2 benchtop)

Ultraviolet A light:

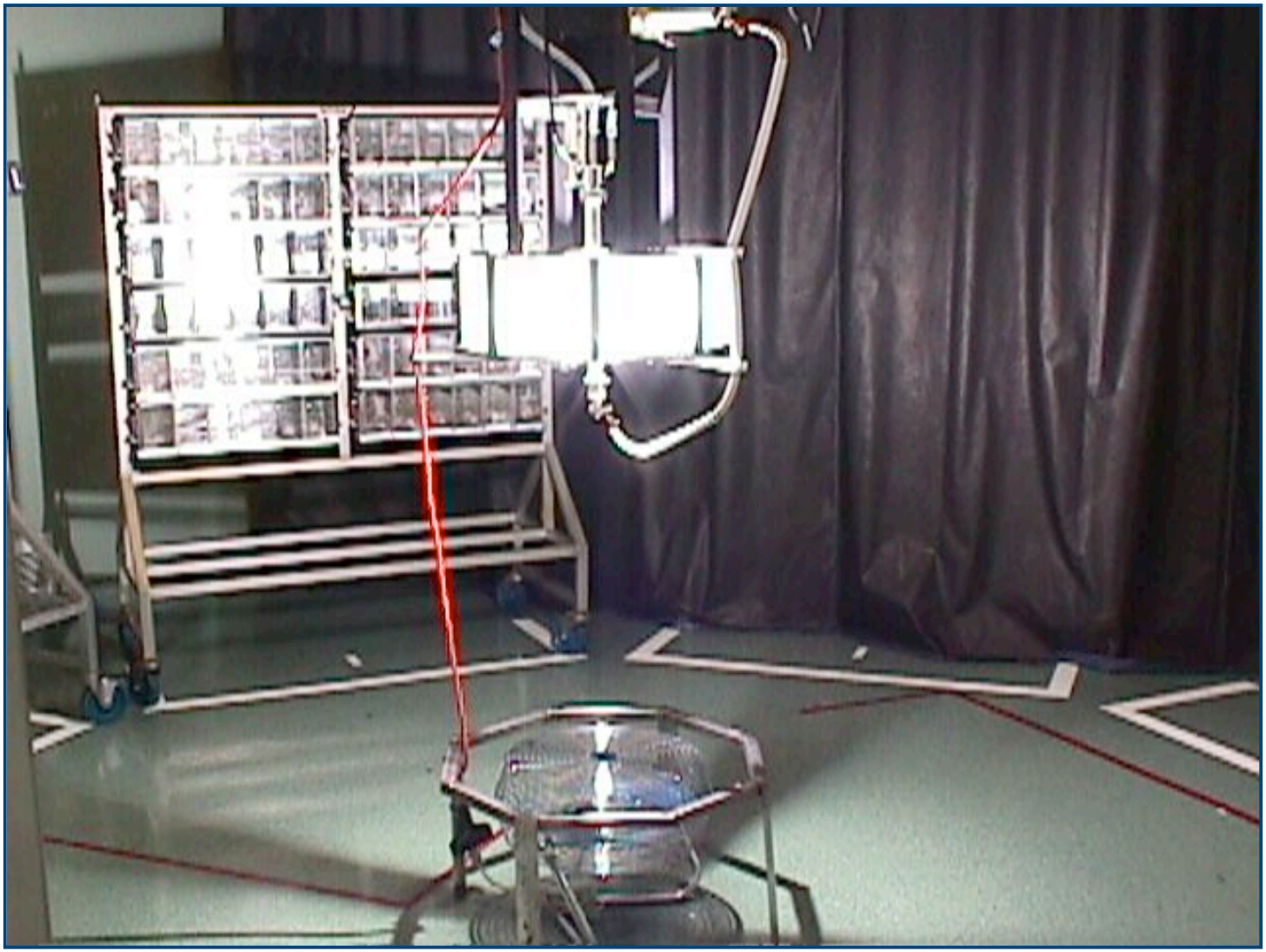
UVA fluorescent lamp exposure
(1 horizontal, 1 vertical, 2 benchtop)

Nd:YAG laser (1064, 532, 355, 266 nm)

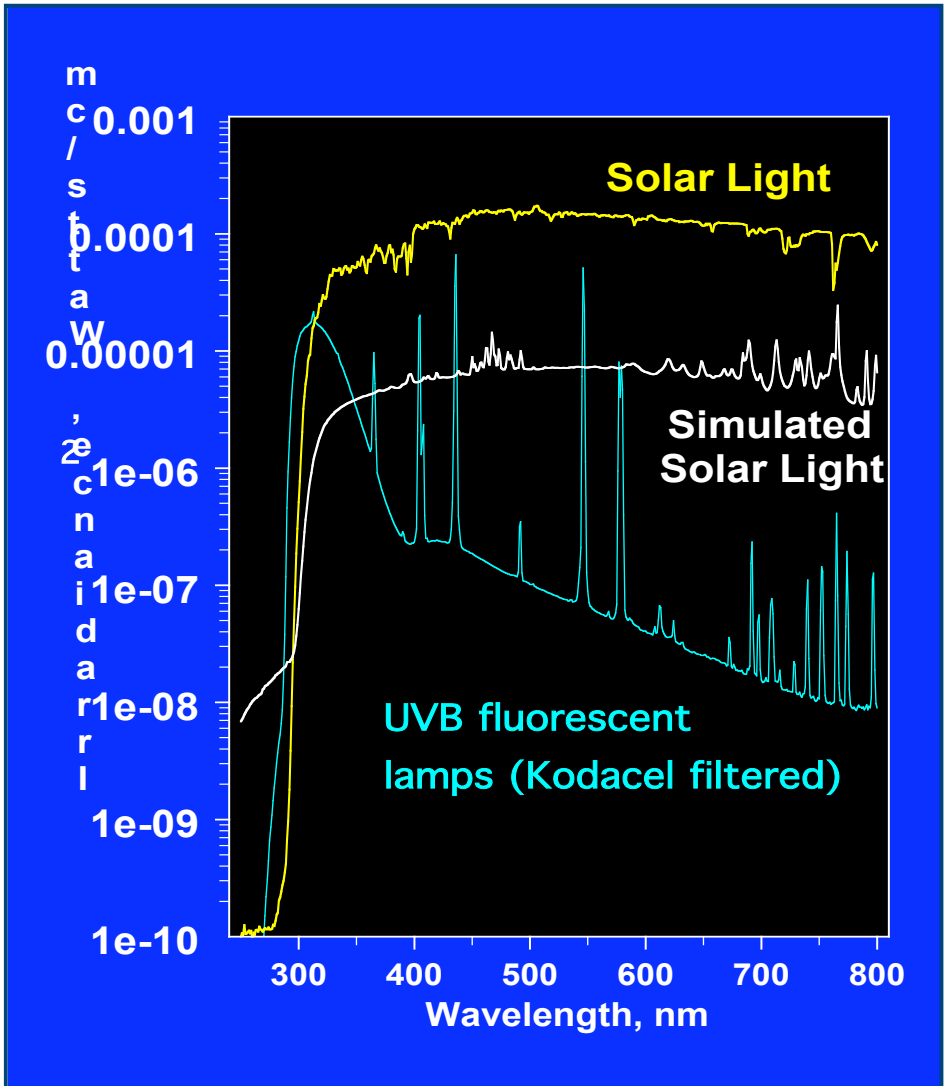
6.5 kW XENON ARC SOLAR LIGHT SIMULATOR - HORIZONTAL



EXPOSURE OF MICE TO 6.5 kW LIGHT

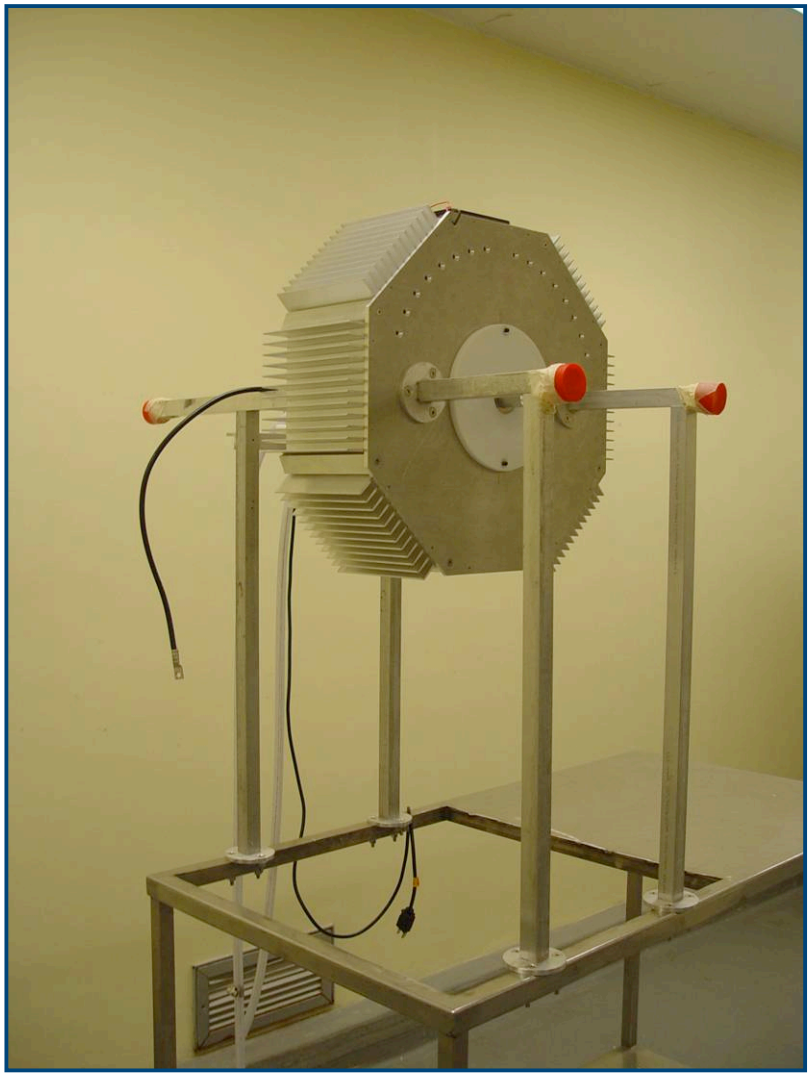


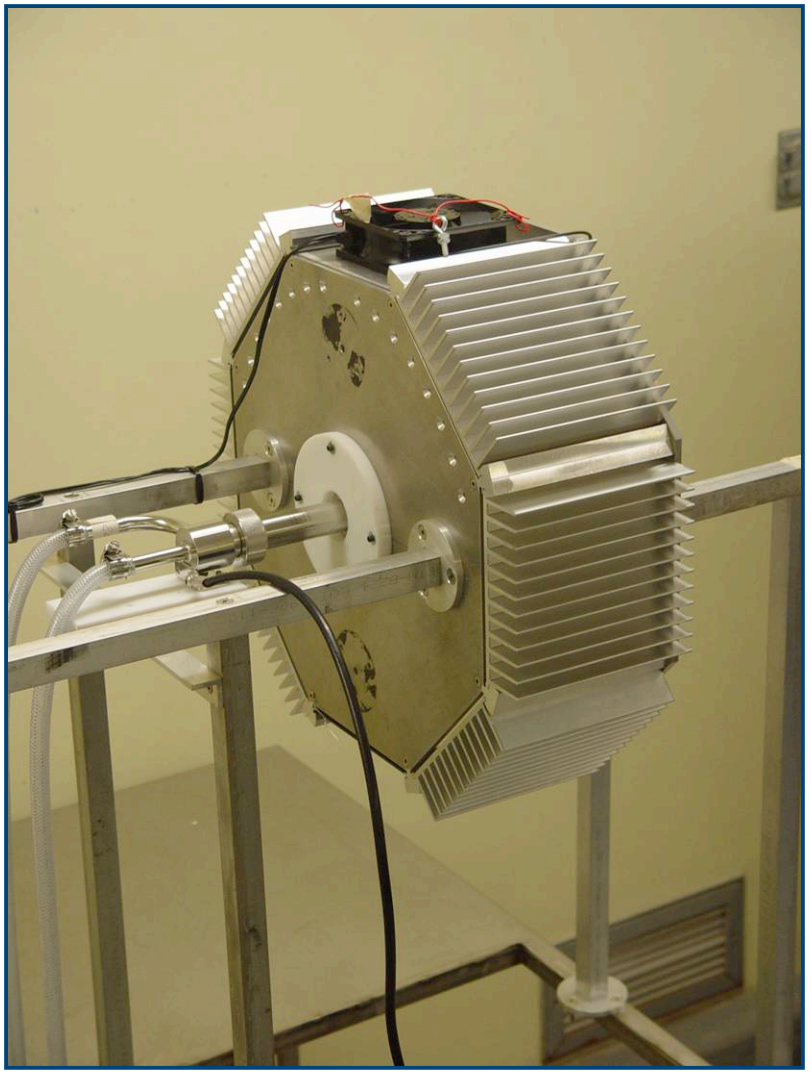
SPECTRUM OF 6.5 kW XENON ARC LIGHT



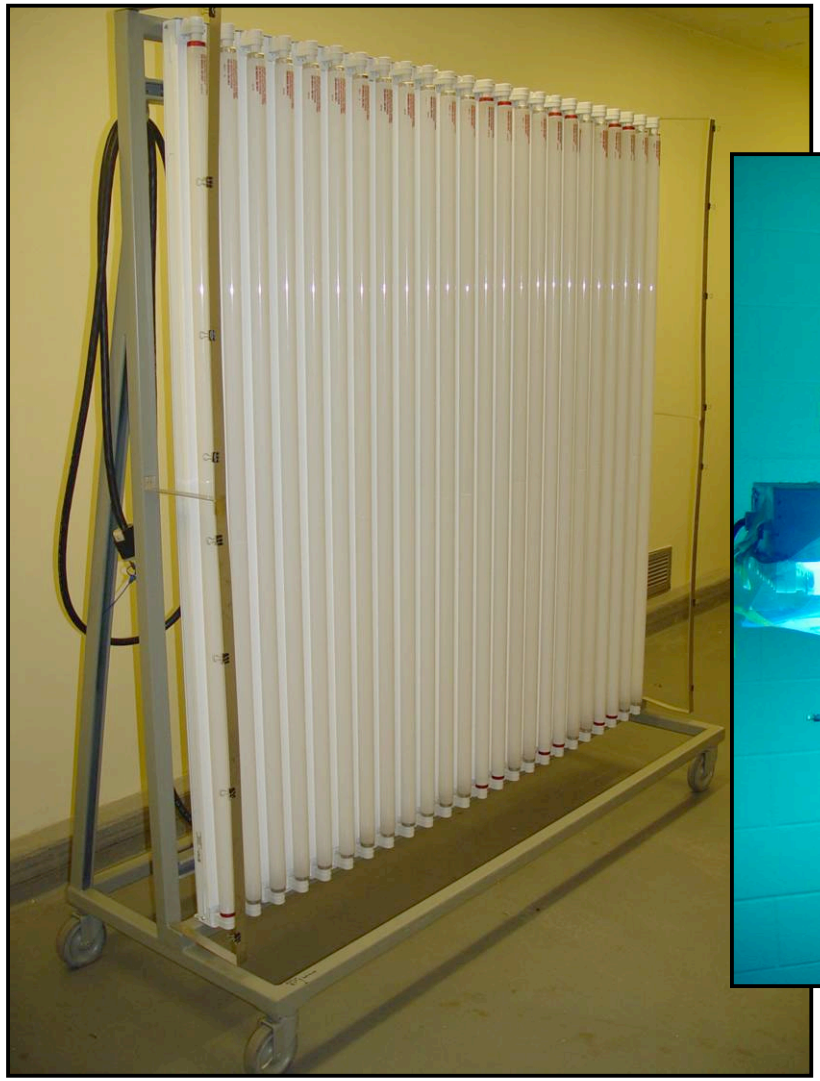
Spectrum of xenon arc light is more similar to sunlight than commonly used fluorescent sunlamps.

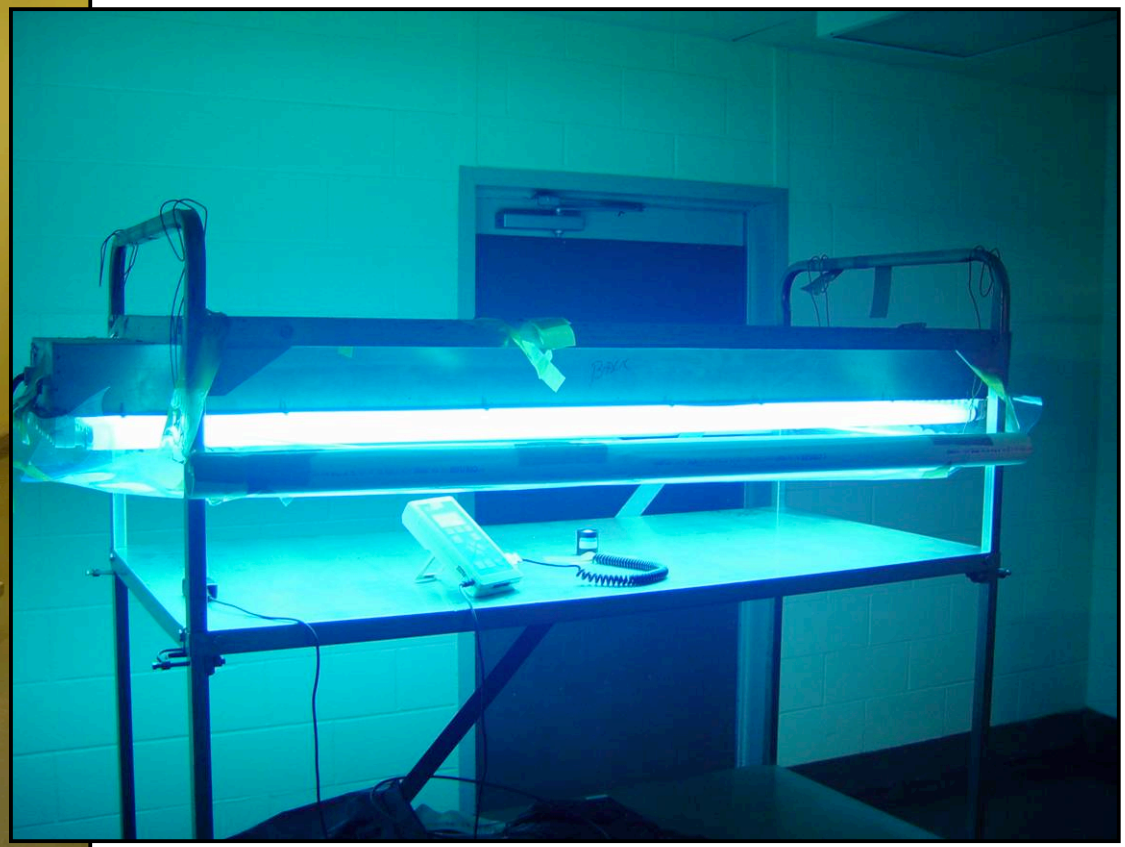
6.5 kW XENON ARC SOLAR LIGHT SIMULATOR - VERTICAL





UVB FLUORESCENT LAMP UNITS





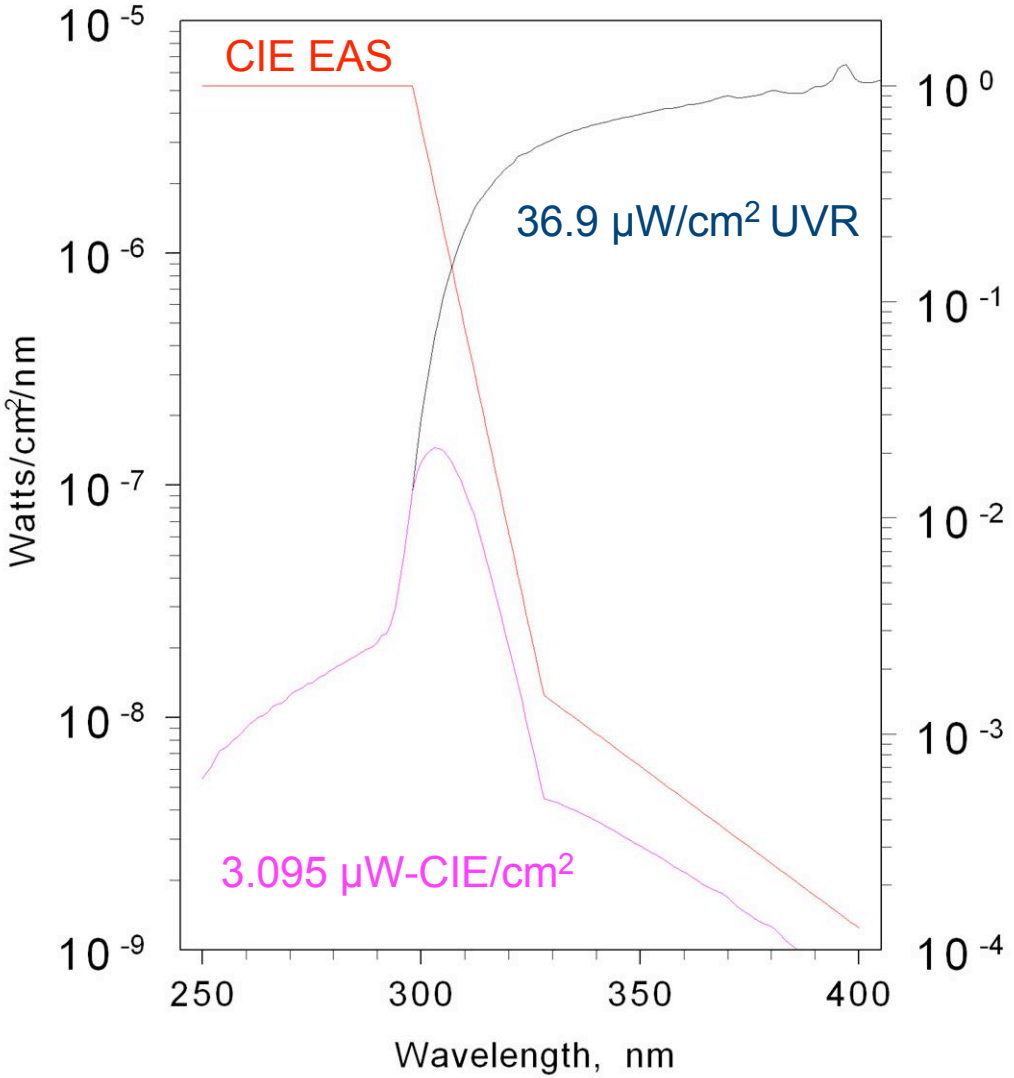
UVA FLUORESCENT LAMP UNITS

DOSIMETRY

Erythema Action Spectrum (red line) represents the relationship of erythema to the wavelength of light.

Multiplication of the 6.5 kW light spectrum (blue line) and EAS generates the weighted irradiance (magenta line).

3.095 μW-CIE/cm^2 x 60 sec = 186 μJ-CIE/cm^2/min



DOSIMETRY

Typical photocarcinogenesis doses of simulated solar light are 0.3, 0.6, and 0.9 $MED^{instrumental}$:

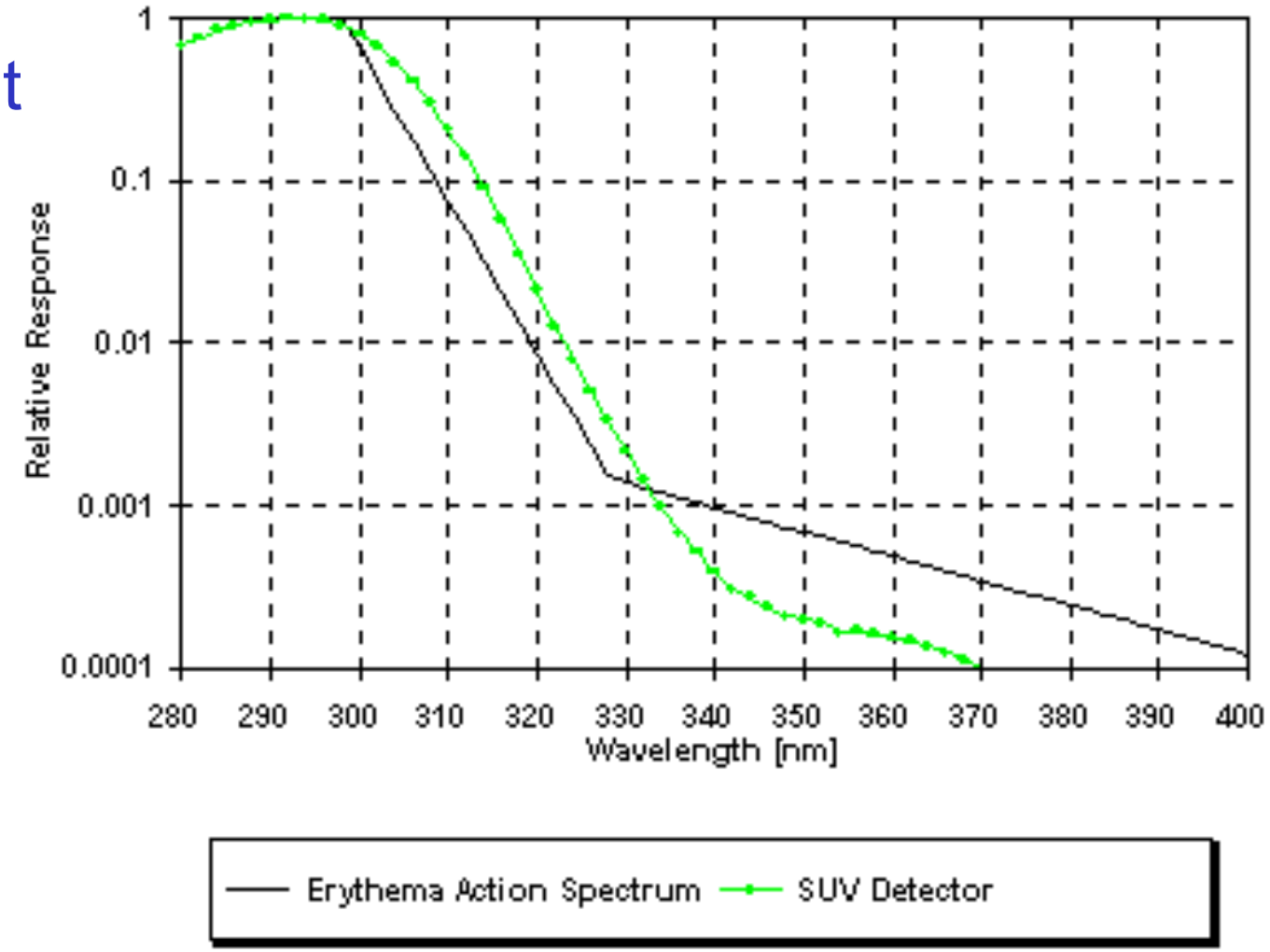
0.3 $MED^{instrumental}$/day = 6.55 mJ-CIE/cm^2/day

0.6 $MED^{instrumental}$/day = 13.7 mJ-CIE/cm^2/day

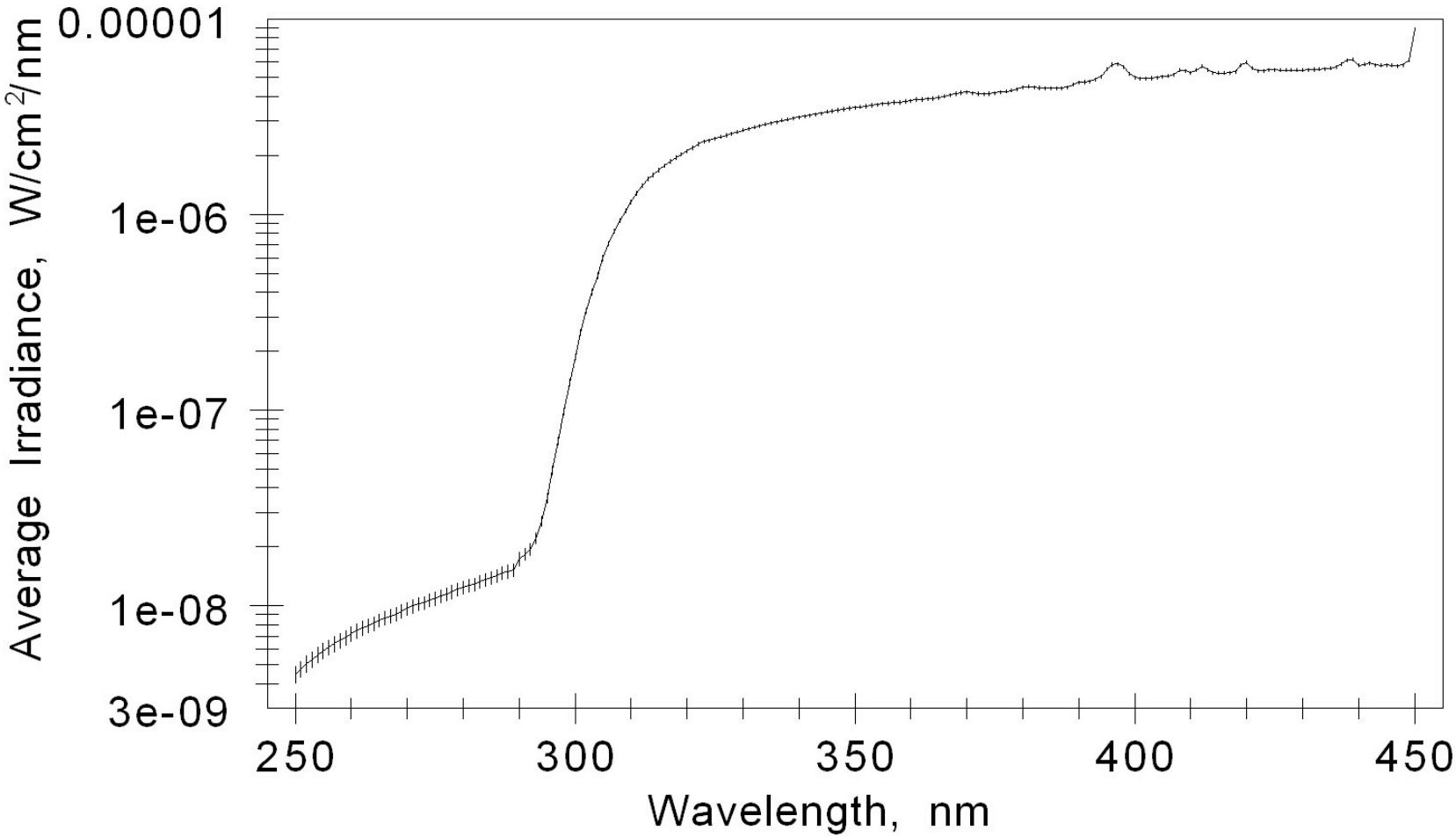
0.9 $MED^{instrumental}$/day = 20.55 mJ-CIE/cm^2/day

DOSIMETRY

The Solar Light PMA 1101 dosimeter has approximately the same spectral response as skin to erythema



AVERAGE SPECTRUM OF LIGHT IN STUDY TR524



AVERAGE DOSES OF LIGHT DELIVERED IN TR524

	FEMALE	MALE
0.3 MED^{i}/day 34.25 mJ-CIE/cm^2/week	100.05%	100.26%
	100.24%	100.23%
0.6 MED^{i}/day 68.5 mJ-CIE/cm^2/week	100.06%	100.06%
	99.97%	100.13%
0.9 MED^{i}/day 102.75 mJ-CIE/cm^2/week	100.01%	100.06%

ANIMAL HUSBANDRY

Test animal

SKH-1 (hr^{-}/hr^{-}); Tg.AC;
TP*ras*(+),p16/INK4a(+/-)

Stainless steel mouse housing/exposure racks

90 units

Automatic watering system for racks

6 rooms, 14 racks/room

Quarantine facility for receipt of off-site mice

NCTR breeding facility

F344, $B6C3F_1$, TP-*ras*(+),p16/INK4a(-/-)]

SKH-1 (hr¯/hr¯) MOUSE

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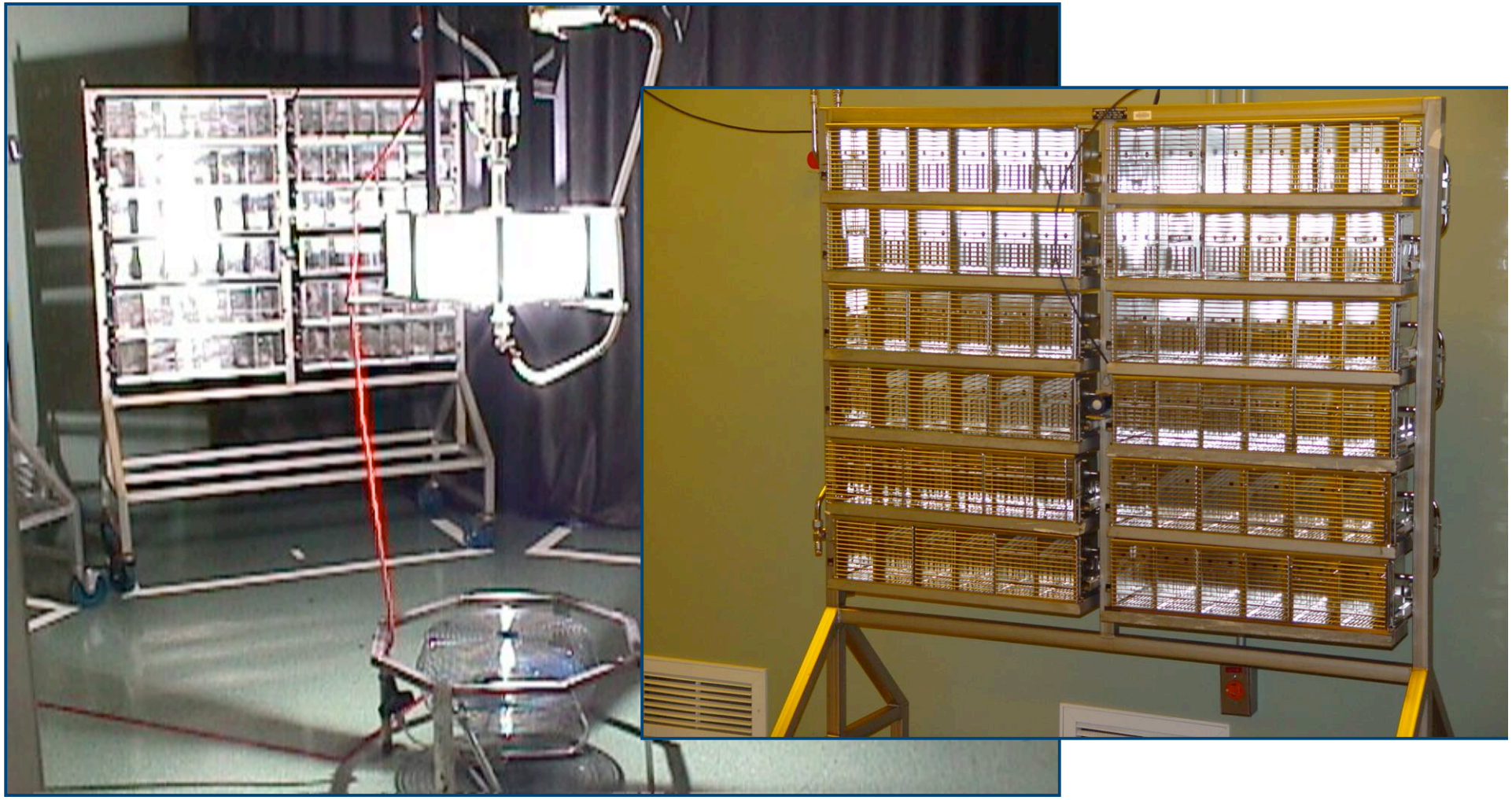
ANIMAL HOUSING/EXPOSURE

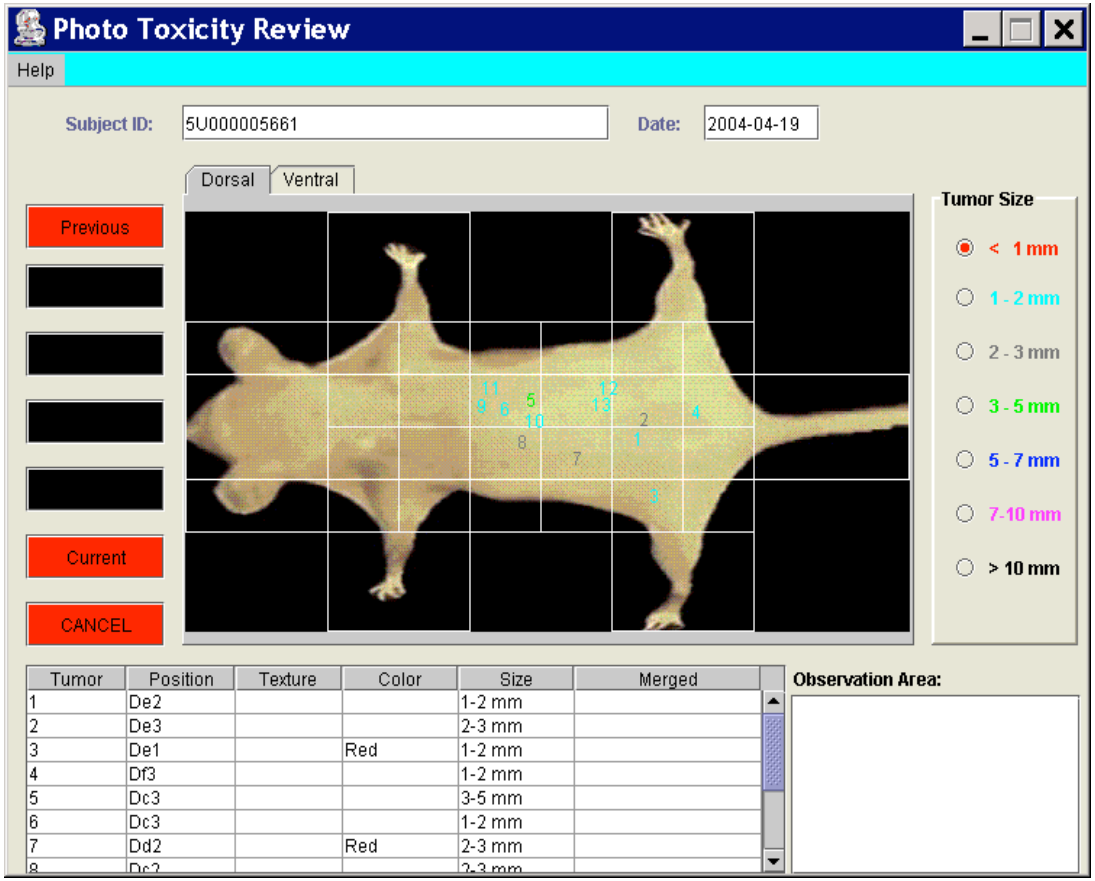


MULTIGEN DATABASE FOR STUDY SUPPORT

Animal ID, location, test group
Operator ID and location
Animal treatment (*e.g.* cream, light)
Twice daily checked (am, pm)
Weekly animal weights and clinical observations recorded
Tumor size and location (weekly)
Animal disposition

MEASUREMENT OF TUMOR SIZE

Past – Caliper-based measurement, entry into animal database system.

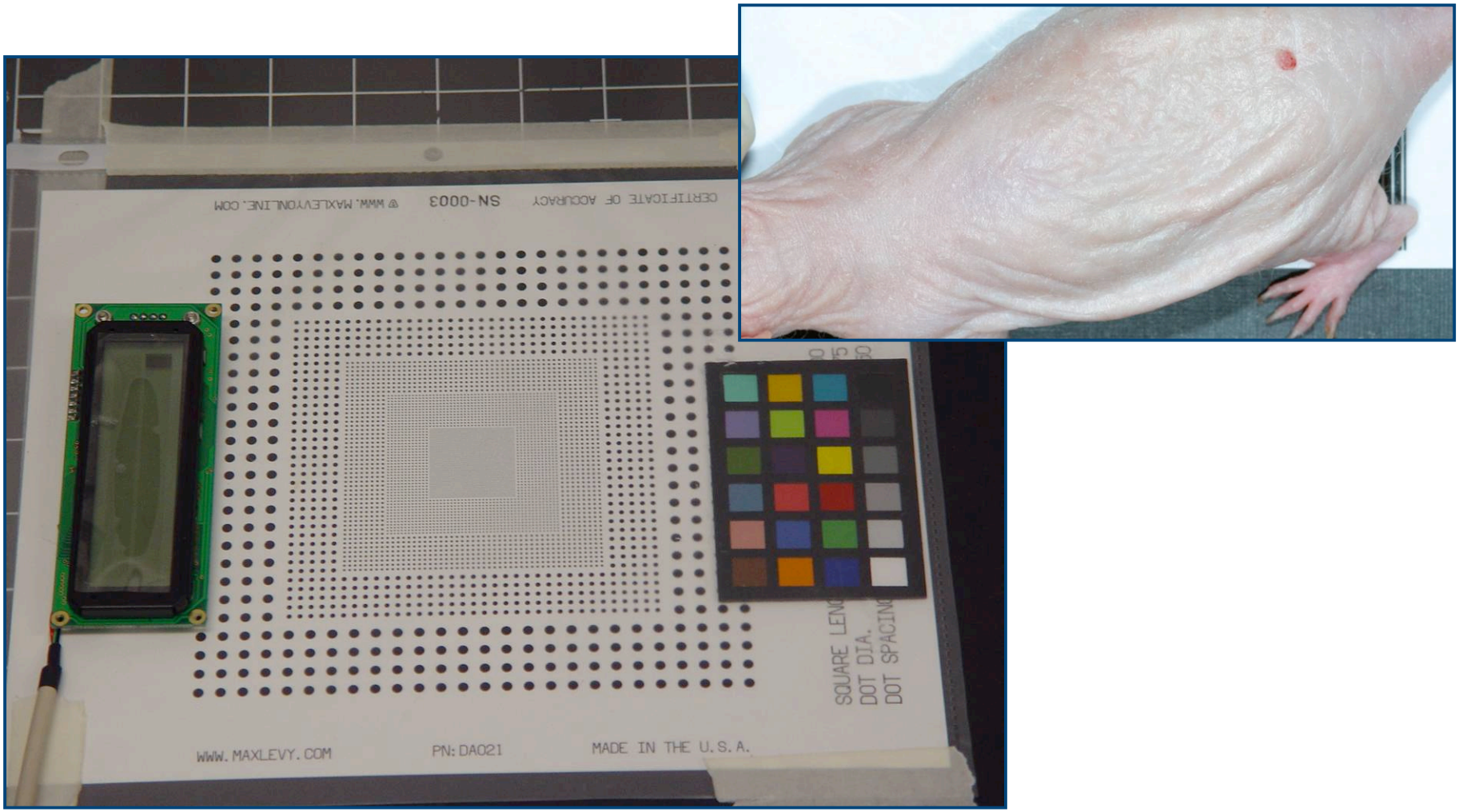


MEASUREMENT OF TUMOR SIZE

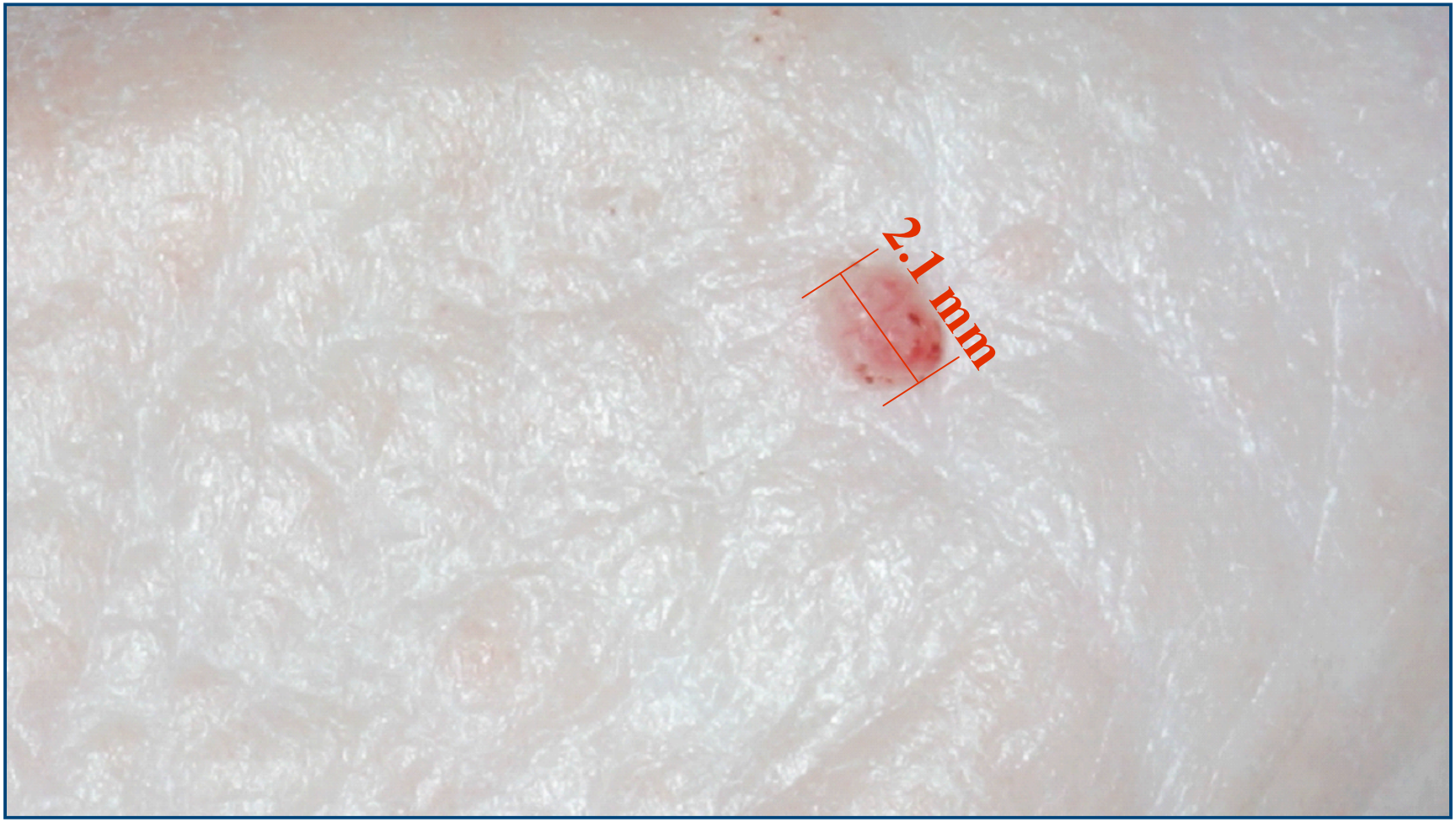
Present –
-digital image of animal;
-downloaded into MultiGen database;
-skin lesions measured using calibrated image analysis software.

Results in:
-improved accuracy, and
-ability for reexamination of tumor size
(or aspect ratio, surface area, etc).

DIGITAL IMAGE SYSTEM



MEASUREMENT OF TUMORS: CALIBRATED SOFTWARE



STUDY SUPPORT

- Animal husbandry
  - Div. Veterinary Services, Animal Care
  - Contractor, NCTR IACUC
- MultiGen database
- Quality Assurance Unit
- Pathology
  - Necropsy, histopathology, tumor images, immunohistochemistry, TDMS
- Statistics
  - Div. Biometry and Risk Assessment, Statistics Contractor
- Facilities, maintenance

STUDIES IN NCP

Alpha and beta hydroxy acids (*TR 524*)
Aloe vera (*PWG, fall 2006*)
Retinyl palmitate (*PWG, spring 2006*)
Furocoumarins (oxypeucedanin) (*completed*)
Nanoscale materials, dermal penetration/toxicity (*in progress*)
Tattoo inks (*peer-review publications; in progress*)
Mouse melanoma model (*peer-review publications; completed*)

FUTURE DIRECTIONS

Future studies

- Nanoscale material tumorigenicity in Tg.AC
- Permanent makeup ink/pigments
- Tattoo ink photocarcinogenicity

Research and support

- Biomarkers of skin cancer development,
  - ACB-PCR *p53* mutations, gene expression (RNA, protein)
- Molecular pathology

NTP Center for Phototoxicology

… meeting the electromagnetic radiation research and testing needs of the NTP and FDA.